

F.G. Hopkins (1938)

BIOLOGICAL THOUGHT AND CHEMICAL THOUGHT

A PLEA FOR UNIFICATION

The Linacre lecture for 1938 delivered at Cambridge on May 6th,

BY

SIR FREDERICK GOWLAND HOPKINS, O.M.,
F.R.C.P., F.R.S.

PROFESSOR OF BIOCHEMISTRY IN THE UNIVERSITY OF CAMBRIDGE

Reprinted from THE LANCET, May 21st, 1938, p. 1147

WELLCOME INSTITUTE LIBRARY	
Coll.	wellcome
Coll.	pam
No.	QU 4
	1938
	H79b



22500887617

BIOLOGICAL THOUGHT AND CHEMICAL THOUGHT

A PLEA FOR UNIFICATION

IN preparing this lecture I have yielded to a temptation excusably felt I think by one who sees near at hand the close of an active career. To compare the present with the past in the field of his own activities, and to advertise the progress he himself has seen, is for such a natural impulse where opportunity is offered. If however I now yield to that impulse it is not without an ulterior aim.

No one with adequate knowledge will deny that the subject of biochemistry during recent years has shown itself to be a fertile field, at least for those intent on gathering a harvest of facts. The recruitment of labourers to that field has lately grown, and is still growing so fast that the facts garnered seem already overwhelming. In the minds of some at least, the question still arises: What (practical applications apart) is likely to be the ultimate significance for biological science of these myriad chemical facts? It is part of my intention to attempt in a very limited and humble way to make some appraisal of this significance.

To this end then I may first be allowed to estimate in fewest possible words the essential nature, as it appears to me, of the progress which biochemistry has made since I first had concern with it just fifty years ago. I can of course do no more than illustrate that progress with a few examples, dealing with its kind rather than its extent. I ought perhaps to say at once that when throughout this lecture I refer to its progress, I shall mean the advances it has made as a branch of fundamental scientific inquiry. Its practical applications in the field of Medicine and elsewhere are to-day not without general recognition. On these I will not dwell on this occasion.

OUTLOOK OF THE BIOCHEMIST

In my own earliest days all who hoped to apply chemical methods and chemical thought to biological

problems suffered certain noteworthy disadvantages. First they obtained little help and no great sympathy from the organic chemists of the day, whose interests had for the most part wandered away from the study of natural products ; then they felt acutely the lack of an adequate knowledge of colloids, for colloid science had been completely neglected after the pioneer studies of Thomas Graham, then thirty years old, and, again, they had yet to develop adequate methods for the service of what they conceived to be their own special needs. All disadvantages of this kind have happily disappeared to-day.

In those earlier days, however, the would-be biochemist suffered an inhibition of a different kind which, to some at least, myself among the number, was real. We had to face the distrust of the guardians of a territory which we hoped to invade. I am thinking in particular of the attitude of many experimental biologists, whose work just then was already revealing knowledge of great significance. Let me say here that encouragement for the chemist was not lacking from leading physiologists of that day ; many of these believed that their own subject called for development on its chemical side. It was indeed that belief in the mind of one of the most eminent among them, the late Sir Michael Foster, which gave to me the opportunities I have for so many years enjoyed in Cambridge. But the professional interests of the physiologists were naturally centred mainly on the functioning of organs, or on the metabolism of the animal body as a whole, while the particular hope of the ambitious biochemist, when his thoughts ran ahead, was that he might contribute to knowledge of the nature of living stuff itself. With that ambition it was natural that he should endeavour to learn all he could about the known behaviour of living unit systems ; the visible reactions, for instance, of cell protoplasm when submitted by experiment to varying conditions. There was here relatively little help from the histology of dead tissue cells as taught in the schools of anatomy and physiology. Rather had he to turn to facts revealed in the field of general biology and especially in that of experimental cytology. The remarkable potentialities of protoplasm then already being revealed by experiment strengthened the growing reaction against the mechanistic views which had held sway in the middle of the century, and stiffened the biologist in the belief that biology must remain a science *sui generis*, with

its own primary concepts and its own ultimate units of significant structure. This meant the recognition of a grave breach in the unity of science, disturbing to chemical thought, and discouraging to the higher ambitions of the chemist.

The modern biochemist, rightly or wrongly, has gained in self-confidence, but it is well for him to remember that a conviction of his inability to contribute anything to the fundamental realities of biology is the basis of a definite philosophical outlook still attractive to the minds of not a few.

In an endeavour to illustrate the kind of progress biochemistry has made in my time and, if I can, its significance, I might have chosen almost any out of very many aspects. I have decided to make reference to some which to me, at least, seem characteristic. They are aspects which, in general outline at least, are among the most familiar, yet I feel that they, perhaps more than any other, have altered my own outlook. I will refer to our realisation of the fact that the phenomenon of *catalysis* is universal and fundamental in the scheme of living Nature, and further will remind you that the frank influence of molecular structure is exerted to the full in every living system. I will then ask you to remember the circumstance, now in a general sense so familiar, that the normal progress of events in every living system calls for the presence of a number of highly specific substances, each exerting its own peculiar influence in a quantity which is almost infinitesimal; implying that the chemical equilibria on which life depends may be balanced, as it were, on pin points.

CONCEPTIONS OF CATALYSIS

The thought of many biologists—in so far as it has concerned itself at all with the old problem as to why, in the conditions found in living tissues, chemical reactions involving stable substances proceed at all—has been content, it has seemed to me, to find a solution in the esoteric and irreducible properties of protoplasm, or in those of (to the chemist) equally unapproachable “living units” within the cell. This is not necessarily a vitalistic view, but may involve rather a disbelief in the ability of chemical methods to produce any adequate analysis. A great change in the outlook for biochemistry came, however, when it was first fully realised that the events of

metabolism proceed in fact because they are catalysed, and on lines not differing in fundamentals from those of catalysis as observed in the inorganic world.

I sometimes find it hard on looking back to realise that, though the catalytic activity of enzymes outside the cell had been long known, the belief that they play so dominant a part in the interior economy of every living system was not reached till the very end of the last century. Even then the conception of intracellular enzymic activities was distasteful to many, and by not a few contemporary writers their real significance was doubted, or the extent of their influence minimised.

I will now discuss with all possible brevity certain current conceptions in the field of what is often spoken of as biocatalysis.

I must first make some reference to the colloidal structures of the cell, on which of course so many of its most fundamental properties and its visible behaviour depend.

When during earlier stages in the development of colloid science its data were applied to living systems, there was much emphasis on the general properties of surfaces and interfaces; but there was then but little understanding of how diverse and specific these properties may be. When thinking of those myriad chemical reactions (essential to the display of life) which simple molecules undergo in the aqueous phases of the cell, some of us were too apt to think of its colloidal complexes as just a special type of apparatus in which these reactions were suitably accommodated. But the recent great advances in our knowledge of surfaces, in particular of what has been called their "molecular anatomy," which in this or that case endows a surface with quite specialised properties, has shown that the due progress of the reactions is very intimately connected with the properties of the colloidal structures. Physical chemistry and organic chemistry here meet together. The remarkable recent increase in our knowledge of the intimacies of complex protein molecules which the application of physical and physicochemical methods is just now providing has here to be remembered. Though colloidal, these large molecules may yet be very "active." Many, if not all, enzymes for instance seem to be specialised proteins, and the isolation of many potent plant viruses, in the accomplishment of which my colleague Mr. N. W. Pirie

has had so large a share, has shown that the active unit in each case is in essentials a complex protein molecule. The view is expressed that even a chromosome may be a unit structure in the form of a large protein molecule capable of a great variety of internal steric variations !

Experimental dealings with enzymes have now produced a vast literature, but I will confine my remarks to those special catalytic agencies which promote the processes of oxidation and reduction, thus making the potential energy of foodstuffs available for the activity of living cells. Some of my own colleagues have made important contributions to this field, and on such an occasion as this I may be allowed the luxury of choosing my illustrations chiefly from results obtained by them.

OXIDATIONS AND REDUCTIONS

All earlier efforts to explain the occurrence of tissue oxidations were directed to the discovery of how molecular oxygen, which vis-à-vis with the tissues is inert, is made capable of reaction. We have still to recognise the importance of oxygen activation, but it is remarkable how prominent in living cells is the additional activation of hydrogen. I must not stop to explain the steps by which realisation of this fact arose or mention the work of able investigators which led to it. In effect it means that the molecules of metabolites may be so affected by contact with special enzymes that hydrogen atoms in their structure are made labile and capable of transference to oxygen, or, and this is important, to other molecules. We now call the enzymes which so mobilise hydrogen by the name of *dehydrogenases*. It is customary and convenient to speak of the substances from which the hydrogen takes origin under their influence as hydrogen donators, and those to which it is transferred as hydrogen acceptors.

It seems sure that the influence of enzyme catalysis is never absent when other accepted criteria of life are present ; or, since the present position of virus studies is making a definition of life even more evasive than it has hitherto been, let us rather say that it is never absent from a system which metabolises. Perhaps the power to metabolise independently is as good a criterion of life as any other. It is of great interest in illustration of this to follow

the display of catalysis in free living unicellular organisms which, unlike the tissue cells of higher organisms, are fated to metabolise and grow in environments which may greatly vary. To the study of enzymes in bacteria, colleagues of mine in the Cambridge School of Biochemistry have made important contributions. Dr. Marjory Stephenson and (formerly) Dr. Quastel, with able collaborators, have worked there in this field for several years, and for me it would be a specially pleasant task to spend an hour in describing their researches, but I can only remark on the significance of some of the results. I must point out, however, that many of these researches have been carried out with the use of a special technique, originating in our department but now freely used elsewhere. This involves a study of events in the external medium induced by the organisms when not growing. In these circumstances the induced chemical reactions can be much more closely studied than when growth is proceeding. For the pathologist and for classical bacteriology, the interest of researches on non-proliferating organisms is at present perhaps remote, but they reveal, as no other technique can so well reveal, how remarkable is the catalytic equipment of these minute living units.

Very striking is the great number of substances, otherwise stable, of which the molecules become activated under the influence of specific dehydrogenases on the surface of a bacterium, thus becoming potential donators of hydrogen in the sense I have mentioned. But the very same surface may also present catalytic mechanisms dealing with hydrogen on quite different lines. Dehydrogenase activity requires the presence of hydrogen acceptors for its display, but a bacterium (*Bacillus coli* for instance) may at the same time be equipped with an enzyme—a *hydrogenlyase*—which so activates the hydrogen in a molecule that it is liberated in free gaseous form; and, yet again, a *hydrogenase* which is capable of activating inert gaseous hydrogen, so that it enters into reactions as a strong reducing agent. My colleagues have shown that bacteria can so control certain chemical reactions in the external medium as to establish true thermodynamic equilibria among the reactants, a point of considerable theoretical importance. The precise means by which anaerobic organisms, those which can dispense with oxygen, and those to which its very presence

is fatal, obtain their energy for growth were long obscure. The Cambridge workers have thrown most interesting light on this problem. They have shown on quantitative lines that if substances are present in the medium in suitable pairs, one capable of acting as a hydrogen donator and the other as an acceptor, the processes of hydrogen transport under the influence of dehydrogenases can itself yield sufficient energy for growth. I will mention just one other phenomenon of quite peculiar interest which my colleagues have illuminated, though they were not the first to observe its occurrence.

While certain enzymes form part of the permanent constitution of each bacterial species, it would seem that others can be newly acquired as the result of contact with particular molecules in the external medium. These have been called adaptive enzymes in contrast with those which are constitutional. To take an instance which in particular has been studied in my department: it has been long known that certain bacterial cultures can break down formic acid into carbon dioxide and free hydrogen. If *Bacillus coli* (say) be first grown in a broth medium completely free from formic acid, it is found, when transferred to a simple medium containing the acid, to lack all power to decompose it, whereas a culture identical in origin but grown in the presence of the acid, is afterwards found, even when not growing, to decompose it vigorously. This is a striking phenomenon which should be borne in mind when we try to form a picture of how enzymes take origin during the growth and development of living cells in general.

There is at least some evidence that adaptive enzymes may appear de novo in the tissue cells of animals as a consequence of some change in the constitution of their internal environment. I do not think it over-bold to believe that here, in elementary form, we have a factor contributing to that fundamental quality of living beings, the power of adaptation. It is sure that chemical adaptations, great or small, accompany all adaptations in form and function. Comparative biochemistry and all that is special in the chemistry of individual organs make this sure.

The complexity of the catalytic equipment at such apparently low levels of organisation as that of the bacteria is certainly a striking thing. Dr. Stephenson has pointed out, I think rightly, that we should

not be led by teleology to believe that every one of the specific mechanisms we can demonstrate to be present in a given organism is necessarily employed in its current maintenance. It is not to be denied, on the other hand, that for free living organisms which may have to adjust to great variations in their growth media such a wide equipment has great survival value.

As you will know, much study through the years has been given to the activities of that other type of unicellular organism, the yeast cell, and to the successive chemical changes involved in alcoholic fermentation. I should have liked to dwell a little on these if only in illustration of the significant circumstance that specific catalysts can direct, as well as promote, reactions. The enzyme equipment of the yeast cell is such that, by it, sugar is converted into alcohol and carbon dioxide. On the other hand such is the equipment of animal tissues that they convert the same sugar in similar circumstances to lactic acid. The directive influence of enzymes is an important element in their activity as contributing to the factors of chemical organisation in the cell. I must, however, say no more about the yeast cell, intensely as its activities have been studied since the days of Pasteur.

In the green plant enzymic activities are prominent and significant enough, but their organisation is much modified by the coexistence of the chlorophyll function.

STAGES IN OXIDATION

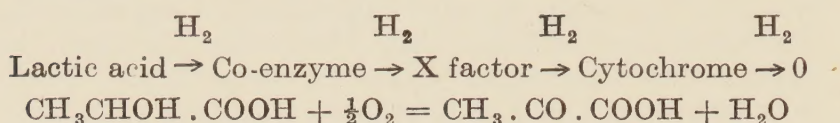
But I must rather turn to the mechanisms involved in the liberation of energy in animal tissues. Here again the mobilisation of hydrogen, and therefore the activity of dehydrogenases, is an outstanding phenomenon ; but here we meet with agencies distinct from the enzymes proper, which with the enzymes form catalytic systems. Such systems may indeed be universal in biocatalysis, but they have been so far most clearly revealed in studies of animal tissues. To their study the Cambridge School, and especially Drs. M. Dixon and D. E. Green, with their collaborators, have contributed much of importance. The following are the essentials of what we know to-day about the more typical of these systems.

It has become clear that, in the tissues, energy is not made available by a single oxidative event,

but more gradually in a series of steps or stages. We picture as being first displayed the activity of the enzymes proper. These are dehydrogenases which mobilise hydrogen in the molecules of metabolites derived from food-supplies. But on its way to oxygen this hydrogen finds an interrupted path. It is transferred in linked stages to a series of specific molecules which, as parts of catalytic systems, are maintained in low concentrations as permanent constituents of living cells. Each of these having acted as the hydrogen acceptor at one stage becomes the donator at the next stage; that is to say, these specific "carriers" of hydrogen, as we may call them, are capable of alternate and reversible processes of reduction and oxidation. Oxygen itself at the end of the series becomes in a somewhat special sense the final hydrogen acceptor. The dehydrogenases themselves would seem to be specialised proteins with highly specific relations. Each one can activate one particular metabolite and one only. This circumstance is highly characteristic of the systems we are considering. In many of these systems, and perhaps in the majority though not in all, the first hydrogen acceptor in the series has relations with the enzyme which are particularly intimate. It is known as a *co-enzyme*. We know of two such at least, each with specific relations. The essentials of their molecular structure are now fortunately known, and their study is dealing with a growing point in our knowledge of cell catalysis.

Another carrier (to be mentioned later) varying in nature in different systems may intervene between the co-enzyme and the penultimate member of the transport series, which is the cytochrome C of Keilin. This most interesting cell constituent is an iron-pyrrol compound related to blood pigment, though exercising so different a function. It is capable, like the other carriers, of reversible reduction and oxidation, and these processes involve a change of spectrum which fortunately can be observed during the life of the cell. Now the combined activities of the agencies previously mentioned reduce the cytochrome molecule with the hydrogen they transport, and the latter is then oxidised by the oxygen of respiration, though for the accomplishment of this yet another factor is required. The molecular oxygen must first be activated, and this is brought about by an agent which I think should be known as the cytochrome oxidase.

The following diagram sums up the relations of all these factors in a particular case. It illustrates the oxidation of lactic acid.



It is clear then that for mobilising the hydrogen of diverse metabolites there are equally diverse mechanisms, and diverse paths along which the hydrogen is conducted to a place of meeting with active oxygen. It is of interest to note that some of these paths converge to join a final common path to oxygen provided by cytochrome. All this complexity gives us a glimpse at least into the organisation of events in the cell. If the only activation involved were that of oxygen itself, biological oxidations could not be so regulated, so specific, and so organised as we know they must be. Moreover, the gradual liberation of energy in successive stages, rather than only at a stage involving the union with oxygen, would seem to be a related aspect of biochemical organisation.

You will realise that I have told you only a part of a large story. In dealing with the oxidation of hydrogen, I have omitted for instance all mention of the origin of the respiratory carbon dioxide. I find I must leave that side of the story without discussion.

A tissue which in particular has occupied the labours of many biochemists, among them my colleague, Dr. Dorothy Needham, is muscular tissue. Indeed the labour spent on revealing the nature and sequence of the chemical events within muscle-fibres has been prodigious. The facts won are so numerous that I must be content to give them the barest reference. They relate chiefly to the successive changes which set free that proportion of the potential energy contained in the carbohydrate stores of the muscle, which is liberated in the absence of oxygen. A number of specific enzymes are concerned, but what the study of muscle has in particular revealed is that certain organic molecules only interact and only undergo certain kinds of enzyme-catalysed changes when they exist in combination with phosphoric acid. The transport of the phosphoryl group from molecule to molecule and the probable simultaneous transfer of energy from exothermic

to endothermic reactions, though it does not occur in the carbohydrate metabolism of all tissues, as was first shown by Dr. E. G. Holmes in a study of brain tissue, is a biochemical phenomenon of great significance.

I will refer to studies of enzyme catalysis in just one more field, that namely of embryology. The writings of Dr. Joseph Needham awakened some years ago much general interest in chemical embryology, and his own work with that of his helpers has contributed much to knowledge of the subject. It is fated to become a very fertile field. I have hitherto made no reference to developments in experimental methods, but may refer here in parentheses to the great benefit biochemistry in general has received from the development of accurate micro- and, so called, ultra-micro-analysis. The ability to employ with confidence minute amounts of material in quantitative experiments has made possible the solution of many problems which at one time would have been thought to be unapproachable. I have for instance derived much pleasure from seeing Dr. Needham, with his colleague Dr. Boell, establish significant differences in the respiration of different parts of the gastrula of the embryo by the use of a method in which only a tenth of a milligramme or less of material was employed.

I have so far put before you in barest outlines a few cases illustrating at least the kind—though by no means the extent—of our knowledge concerning mechanisms without which every biological unit would be a static instead of a dynamic system, and a dead system rather than a live one. We have much more to learn concerning the precise nature of intracellular enzymes and their mode of action, but I am sure we are on the right path for reaching that knowledge, and I will again remind you that I myself belong to a generation which began with little or no understanding of such mechanisms; to one like myself the knowledge we now possess seems quite newly won and remarkable even in its present extent.

The aspect of biocatalysis which I will finally emphasise is its specificity, which, though not absolute, is a quality persistently revealed by experiment. Whatever theory of enzyme action we may hold it is sure that the primary happening is the formation of an association between catalyst and substrate, involving some definite relation between structure

in or on the former and the molecular structure of the latter. It is this dominant influence of molecular structure in living systems that I now wish to illustrate further.

I remember that not many years ago a well-known biologist claimed, in a book dealing with cytology, that as protoplasm cannot be an ordinary chemical compound it can exhibit no molecular structure in the sense understood by the chemist. I used not infrequently to hear somewhat similar views expressed. The former part of the above claim is undoubtedly true. The use of the term protoplasm may be morphologically justified, but chemically it denotes an abstraction. It is sure that it is made up of parts in which the influence of molecular structure as understood by the chemist is all potent.

You will, I think, all realise that when physiologists revealed the existence and functions of hormones they not only gave increased opportunities for the activities of biochemists but in particular gave a new charter to biochemical thought, and with the discovery of vitamins that charter was extended. I would suggest also that the revelation of what we have come to know as the humoral transmission of nerve impulses is a confirmatory clause in that charter, and such, no less, is the recognition of "organiser" functions in the realm of embryology.

We have gradually come to learn the nature of a number of substances of relatively small molecular weight, not forming part of the colloidal structures of the tissue, though able to establish temporary relations with these, but existing in true aqueous solution, and so capable of transport in the aqueous phases of individual cells, or in the circulatory fluids of animals and the sap of plants. We know that the properties of each one of these—and they are surprisingly many—may make its influence absolutely essential for the normal progress and organisation of events in this or that living tissue. In their absence disorganisation follows. Characteristic of all these agents is that they function efficiently in amounts which are extraordinarily small.

HUMORAL TRANSMISSION OF NERVE IMPULSES

I will first call your attention to the phenomenon I referred to as the humoral transmission of nerve impulses. It is of exceptional interest and highly significant for my theme. The control of tissue

activities by the nervous system had long seemed to involve influences quite remote from any so strictly chemical as that due to specific molecular structure. However little we knew about the precise nature of the nerve impulse itself, it seemed sure that some transmitted change largely physical in nature reached a tissue from the nerve, and there, though possibly modified in some way at the nerve-ending, directly affected the equilibrium of the tissue. To-day we know that definite chemical happenings intervene. The arrival of the nerve impulse involves the liberation in the innervated tissue of specific chemical substances, and it is to molecular properties inherent in these that the tissue directly reacts. We have gradually learnt this first from suggestions contained in pioneer studies by T. R. Elliott, followed by the brilliant researches of Otto Loewi, and now by recent and more remarkable extensions in the field due to H. H. Dale and his colleagues.

What we know to-day is briefly this : The impulses carried by nearly all the efferent neurones of the peripheral nervous system liberate in the tissues the substance acetylcholine ; the exceptions being those carried by the post-ganglionic fibres of the true sympathetic system ; but these liberate, alternatively, adrenaline. It is the special chemical nature of these two relatively simple substances that determines the effects observed on stimulation of peripheral nerves and constitutes a link between events in the nerve and events in the tissues.

With the discovery of these facts chemistry made an unexpected and impressive appearance in the physiological arena, and not less impressive was its entry into that of embryology when the so-called "organiser" of Speeman was discovered. It then became known that during the growth of an embryo the direct influence of a particular group of cells at the gastrula stage of development in some way induced the progress of further stages. These cells, if taken from one embryo and transferred to some locality in another, exercise their normal influence there, so that in the host certain structures are duplicated. It was striking enough when the proof came that this influence was chemical ; an extract from the cells in question producing exactly the same highly specific results as the presence of the intact cells. To this story the work here in Cambridge of Drs. Waddington and Needham has contributed much,

HORMONES AND VITAMINS

I turn next to the influence of the more typical hormones and of vitamins. There is little justification for making any sharp distinction between them. In different species they have different origins, but their functions seem to be similar in essentials. I cannot of course attempt here any general discussion of their constitution or their individual functions, nor is this necessary for my purpose, though I will presently, with a particular intention, briefly indicate some relations between constitution and function in the case of a few. In the accompanying illustration I have ventured to assemble the structural formulæ of all these influential molecules so far as they are known (some dozen in all), not wishing however that the significance of structural details should trouble those who are not organic chemists but solely to make clear to the eye what for my present theme is so important—namely, the circumstance that great diversity of function goes with a corresponding diversity of structure. It should be remembered that the influence of substances, potent in function while infinitesimal in amount, is not confined to the tissues of the higher animals. Some micro-organisms at least need what may fairly be called a vitamin supply in their growth medium; hormones necessary for growth, of which the chemical nature is now known, function in plants; and some cases of similar influences have been brought to light in the economy of invertebrates, especially interesting being that of certain insects in which growth and metamorphosis are conditioned by hormones produced by a gland situate in the head (Wigglesworth). Such functions it would seem enter widely into the scheme of Nature.

To determine just how these substances exert their potent influence is an immediate task for the biochemist. It is no simple task and has only recently revealed itself as an urgent scientific duty. It has therefore not yet gone far. It is I think sure in advance that their indispensability must be due to the circumstance that like enzymes (though on different lines) they play a dominant part in maintaining the due progress of dynamic events. We have at least some direct evidence for this.

As many here will know, when a man or animal is deprived of a supply of vitamin B₁ the primary effect is disorganisation of events in the nervous system. Now during the stages involved in the

normal breakdown of carbohydrate in the organism the substance pyruvic acid makes a significant appearance. Prof. Peters at Oxford has shown that the brain tissue of an animal which has suffered from a deficiency of this vitamin, unlike the healthy brain, is unable to deal normally with pyruvic acid, which therefore accumulates in the tissue. Experiments in vitro show that most minute amounts of the vitamin, acting perhaps in some essential combination, restore the power of brain tissue and other tissues which lack it, to decide the fate of pyruvic acid. This and other evidence indicates that one function of vitamin B₁ is to play an important part in the control of carbohydrate metabolism.

It has recently been revealed in dramatic fashion that the dire disease pellagra, so prevalent in certain countries, is due to the lack of a substance which has a relatively simple constitution—namely, nicotinic acid. In most minute amounts this can prevent or cure the most severe symptoms of this disease. Nicotinic acid must now be placed in the category of essential vitamins. I will here ask you to recall what I said about the functions of co-enzymes as contributing to the transference of hydrogen to oxygen. Now to the relatively complex structure of co-enzymes the structure of nicotinic acid contributes, forming that part of the whole molecule which is directly concerned in the transport of hydrogen. It would seem as though the ring structure of nicotinic acid is one which the tissues cannot synthesise, though it has important and biochemical functions to perform. It must therefore be supplied in the food. Again there is a vitamin, B₂, or lactoflavin, which is known to be necessary for animal growth. The molecule of this also contains a special ring structure—the alloxazine ring—which again the tissues seem unable to synthesise; hence the need of this vitamin. Now when in metabolism lactoflavin becomes linked up with a specific protein, it also plays, at least in certain cases, a notable part in hydrogen transport, the alloxazine ring being the essential carrier. These few cases show that the influence of vitamins may be exerted amid the dissimulative events which liberate energy; perhaps in the laboratory we have so far only found it in such connexions because it is chiefly there we have looked for it. It seems to me sure however, since a lack of any one among hormones and vitamins involves

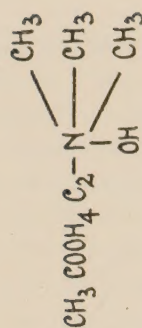
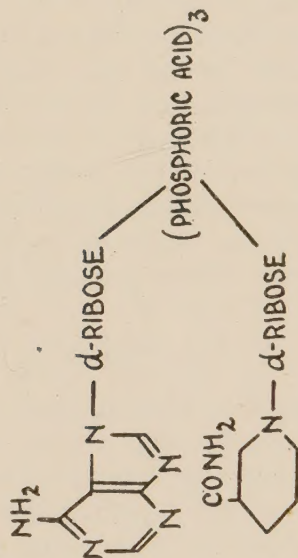
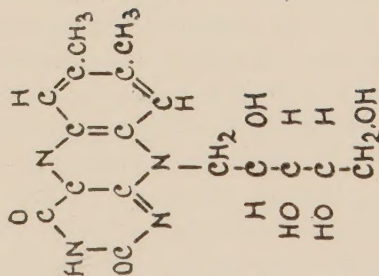
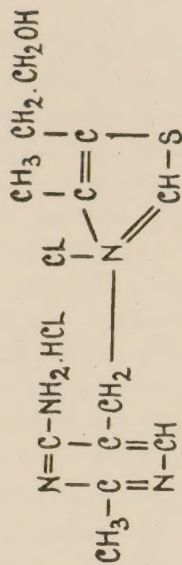
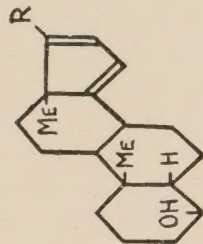
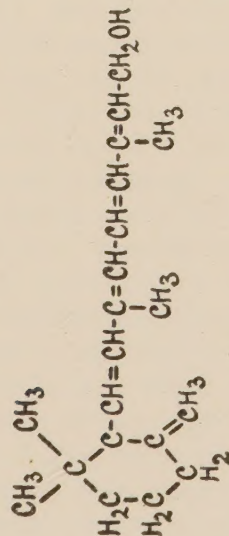
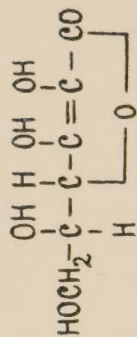
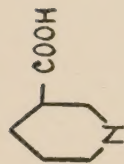
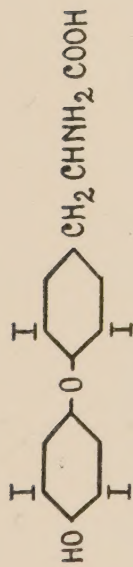
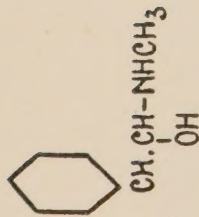
such profound and specific effects on tissue cells in the animal body, that their influence in a chemical sense goes deeper than this, and is somehow concerned with the organisation of reactions in the tissues. In some key positions they must exert a wide control over events.

I have put many facts before you, but they are a very small sample of those available with similar bearings. Many are facts of an order or kind which not so many years ago would have seemed beyond our power to reveal. What for the moment I would emphasise is that they are so frankly chemical that only chemical language can deal with them. Will any intellectual synthesis ultimately make easy a translation into biological terms? What degree of such synthesis may we hope for in the future?

STUDY OF EVENTS IN ISOLATION

I have more than once referred to "organisation." The very word gives pause to the biochemist. If his ultimate aim is to describe adequately a living system in chemical terms, he must face the fact that he is proposing to explore a field in which chemical events are organised with a complexity not thought of in the development of classical chemical science. There are doubtless "higher" levels of organisation in the description of which chemical language can take no direct part. But if we speak of higher and lower levels, we must not do so with the assumption that one is more important than another.

Description at any one level alone will be found to have inherent limitations. At the chemical level many recent studies, apart from those on micro-organisms, have been made on intact tissue cells during true survival life *in vitro*; but those which have thrown most light on the nature of the controlling mechanisms have involved the isolation of such mechanisms. We have isolated nevertheless not structural materials alone but events in progress, events proceeding in space and time, and therefore, as samples, retaining something at least of the nature of the whole. We realise of course that events studied in isolation may be modified when proceeding in the environment of the whole. Our methods of isolation do not, however, create artefacts, though they may lead us to study potentialities rather than actualities. It is part of our task, present and future, to distinguish the latter amid the former.



Above are assembled the structural formulae of a group of substances each of which, owing to its specific chemical nature, plays some dominant part in maintaining the integrity and due progress of dynamic events in living organisms. They are assembled not for insistence on the significance of structural details but only to make clear to the eye how great diversity of function is associated with equal diversity of constitution.

- (1) Adrenaline; (2) thyroxine; (3) nicotinic acid; (4) vitamin C; (5) vitamin A; (6) calciferol, one form of vitamin D, the sterol ring system here shown is also the basic structure of the sex hormones; (7) vitamin B₁; (8) vitamin B₂; (9) co-enzyme II; (10) acetylcholine.

Let it be frankly admitted that biochemical studies have still before them, save in small, though not negligible, part, what I will again claim as their legitimate aim and major task—the endeavour namely to describe biochemical events from the standpoint of their organisation during life. If and when such effort succeeds, and only then, we shall know just how far chemical thought can reach towards a full description of any living unit. Many, and, I think, most to-day, believe that the full description will call in addition for thought of another kind. Nevertheless at any one level of organisation description may have its own measure of completeness.

With regard once more to the present position of biochemistry, let me again remind you that it is only during the last few decades that its pursuits have revealed something of the nature of the individual events which must share in the organisation, and made clear how great is their number. Progress is accelerating and a young science need not fear the law of diminishing returns. Moreover as a borderland science, apart from its own momentum, it is constantly gaining impetus and fresh opportunities from advances made on each of its frontiers. Especially is this true at the present moment.

BIOCHEMISTRY AND BIOLOGY

I chose for this lecture an ambitious title which needs some excuse. You will have realised by now that its terms were meant to apply to a field for thought which, though surely all important and one which, occasionally at least, must occupy the mind of every biologist, is yet, for discussion, a limited one. There are of course, and always will be, great fields of biological endeavour, where no direct contacts with chemical thought are sought or called for; there are equally wide fields where chemical endeavours have no concern with biological thought. It is especially for those who feel an irresistibly strong desire to learn what can be known about the fundamental nature of living stuff, to realise that here two modes of thought make immediate contact. As Prof. James Gray has said, "cytology may rightly claim to be the frontier state in the biological commonwealth, for within its borders biologists and chemists find common ground." Are their differences such that their thought about the living cell must be mutually exclusive; may they not rather, without

either losing its own special character, prove eventually helpful, and even essential each to the other ?

I was a little disconcerted when asked, after the title of this lecture was announced, how I would define biological thought for my purpose, for it has many varieties. What I meant by it as applied in the particular field which I have made the special concern of this lecture, is such thought about a living unit which ignores, or minimises the importance of, those molecular events which must underlie the visible manifestations of its life ; an attitude of mind often based perhaps on a doubt whether any attempt to correlate the molecular with the visible is within the competence of experimental science. Let me add that I have met the same doubt in the minds of some few highly competent chemists. Their view is that biochemistry should endeavour to follow every path that will lead to utility. Such paths are many and open ; let us, they say, do what we know we can do and not follow a will-o'-the-wisp. I cannot agree with this view.

There are however biologists who, with none but friendly feelings for biochemical effort, and by no means excluding its results from their thoughts, yet so fully realise the complexities their own work continues to reveal that they instinctively recoil from chemical approaches that seem too facile.

There is one who, I know, sometimes feels this whose opinion all very greatly respect and value. I mean our own professor of zoology. In his admirable book on experimental cytology, to which I personally owe much, Prof. Gray, while displaying full sympathy with biochemical endeavour, to which indeed he has himself contributed, shows himself rightly concerned to warn his readers against such chemical discussions of the subject as appear to him crude. He will, I know, not mind my quoting some of his words. At one point, irritated perhaps by something recently read, he speaks out sharply. Having discussed some obscure aspects of cell structure he adds "but the position is dark, and placidly to regard the cell as though its mysteries were all but revealed by the magic wand of chemistry, is a sorry tribute to biological facts." And again, "A biological problem disguised by the sparkling terminology of the chemist is too often a pathetic and rather disreputable object." I would fain believe that the chemist—the would-be biochemist at any rate—has modesty enough to disclaim alike the possession

of a magic wand, and the ability to speak a language which sparkles, but I quote these words of our distinguished colleague, realising that he is really much more merciful than they suggest, because they give me an excuse for suggesting that there are problems, essentially I think biological, which are disguised by any language which is not chemical.

I do not think in illustration of what I mean I need do more than repeat myself. With all the events that can be directly observed in living cells, including those truly remarkable occurrences involved in cell growth and division, cell differentiation in development, and the like, which it has been the privilege of classical cytology and especially experimental cytology to reveal, there must be associated molecular events as varied and in some way as controlled as are the visible events themselves. An understanding of these latter presents a problem which, however difficult of approach, is a real problem, and, surely, a biological problem. Only a frank disbelief in any real correlation between the invisible and the visible can remove it from that category. Yet if it is to be discussed it must be in the language of chemistry. Let me just add that there is a view sometimes expressed which I think receives a measure of approval from Prof. Gray. It claims that in cytological phenomena the influence of Form may be more important than that of Composition. If one could think only of static composition this might well be admitted, but biological components are seldom static, and dynamic changes, if they are specific, must be undergone by specific materials. In any case it seems to me that the view fails in certain ultimate issues. It is suggested for instance that the form of a chromosome rather than its chemical composition accounts for its influence. But at such magnitudes Form, as ordinarily understood, merges into molecular structure. Form holds its own, but as molecular form, the shape of molecules, and of this we have knowledge much more objective than was the case a few years ago. As I earlier mentioned, some leading cytologists are even coming to the conclusion that a chromosome is a unit structure and a complex protein molecule. I am not qualified to judge how far such a concept is justified, but if it be so it supports my general theme.

I fully sympathise with the distaste of biologists for facile chemical explanations which are *a priori*, and based, as Prof. Gray says, on "hypothetical

biology." To read their protests is indeed a desirable discipline for the mind of the chemist. I think however that if chemists have sometimes so offended they—professed biochemists at any rate—are much less likely to do so to-day. They are at any rate, be it noted, concerned to offer descriptions rather than explanations.

Prof. Herbert Dingle in his noteworthy book "Through Science to Philosophy," referring to a certain conclusion of his own, remarks "In short, on looking forward with hope to a time when physics and biology will be safely wedded, it suggests that physics should be the proposer who, on bended knee, begs for acceptance, but it does not presume to suggest what name the happy couple should take." Under the head of physics he was doubtless thinking of physical science in general. I should like to find among my audience agreement with my own belief that biochemistry is to-day mature enough to justify such a humble proposal for matrimony, and trust you will share my hope that biology, in so far as it has been coy, will not remain so.

A SCIENTIFIC BORDERLAND

It is an old saying, abundantly justified, that where sciences meet there growth occurs. It is true moreover to say that in scientific borderlands not only are facts gathered that are often new in kind, but it is in these regions that wholly new concepts arise. It is my own faith that just as the older biology from its faithful studies of external forms provided a new concept in the doctrine of evolution, so the new biology is yet fated to furnish entirely new fundamental concepts for science, at which physics and chemistry when concerned with the non-living alone could never arrive. Whether they will prove to be such as to create an intellectual revolution comparable with that due to the development of atomic physics, who shall say? I sincerely believe that such new concepts are there to be revealed, but only perhaps as the result of new intellectual interactions. I speak, as you realise, with a special brief, but I think it is worth your while to consider whether a new line of advance in biology (not of course to the exclusion of many other lines) may not come from researches motivated by a full conviction that each observed event in the complex behaviour of a living system is associated with

equally complex and, surely, equally biological events at the molecular level of its constitution ; and by the further conviction that both its aspects are worthy of equal intellectual concern. We must specialise in our methods, but we should share our interests.

You may ask whether I have in mind any policy which would encourage the intellectual approaches I have been advocating. It may be that they would be helped in the future by some modifications in present educational policy, but I will not enlarge on such a matter here. The main thing to hope for is the establishment of favourable mental attitudes.

In concluding my remarks I would like to take this exceptional opportunity for expressing a hope sincerely felt. As one shortly to leave the field of biochemical endeavour, I hope that my younger friends and colleagues will always justify their special designation and strive so far as is humanly possible to be biologists as well as chemists. As an ideal this is not easy of attainment, as I know well ; but every effort towards it will increase the interest and the value of the work before them.